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THE MERCK MANUAL

OF DIAGNOSIS AND THERAPY

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glucose tolerance (eg, glucocorticoids) or increase fluid loss (eg, diuretics). NKHHC can also be induced by peritoneal dialysis or hemodialysis, by tube feeding, and by large IV glucose loads.

The consistent and diagnostic features of NKHHC are CNS alterations, extreme hyperglycemia, dehydration and hyperosmolarity, mild metabolic acidosis without marked hyperketonemia, and prerenal azotemia (or preexisting chronic renal failure). The state of consciousness at presentation varies from mental cloudiness to coma. In contrast to DKA, focal or generalized seizures may occur. Transient hemiplegia may occur. The plasma glucose is usually in the range of 1000 mg/dL (55.5 mmol/L) (much higher than in most cases of DKA). The calculated serum osmolality on admission is about 385 mOsm/kg, whereas the normal level is about 290 mOsm/kg (see Ch. 12). Initial plasma bicarbonate levels are slightly depressed (17 to 22 mmol/L), and the plasma generally is not strongly positive for ketones. Serum Na and K levels are usually normal, but BUN and serum creatinine levels are markedly increased.

The average fluid deficit is 10 L, and acute circulatory collapse is a common terminal event in NKHHC. Widespread in situ thrombosis is a frequent finding on autopsy, and in some cases bleeding ascribed to disseminated intravascular coagulation or gangrenous-appearing digits has been observed.

Treatment

The immediate aim of treatment is to rapidly expand the contracted intravascular volume to stabilize BP and to improve circulation and urine flow.

Treatment is started by infusing 2 to 3 L of 0.9% sodium chloride solution over 1 to 2 h. If this stabilizes BP and circulation and restores good urine flow, then the IV infusion can be changed to 0.45% sodium chloride solution to provide additional water. *The rate of the 0.45% sodium chloride solution infusion must be adjusted in accordance with frequent assessments of BP, cardiovascular status, and the balance between fluid input and output.* **K replacement** is usually started by adding 20 mmol/L potassium as a phosphate salt to the initial liter of the IV-infused 0.45% sodium chloride solution, provided urine flow is adequate and the resulting initial rate of K infusion does not exceed 20 to 40 mmol/h.

Insulin treatment should not be aggressive and may be unnecessary because adequate hydration will usually decrease plasma glucose levels. Patients with NKHHC are often very sensitive to insulin, and large doses can precipitously decrease plasma glucose. A too-quick reduction in osmolality can lead to cerebral edema. However, many obese type II DM patients with NKHHC require larger insulin doses to reduce their marked hyperglycemia. If insulin is administered, 5% glucose should be added to the IV fluids when the plasma glucose reaches approximately 250 mg/dL (13.88 mmol/L) to avoid hypoglycemia. After recovery from the acute episode, patients are usually switched to adjusted doses of subcutaneous regular insulin at 4- to 6-h intervals. Many patients who are treated effectively for NKHHC with insulin initially may maintain their glucose control with diet or with oral hypoglycemics.

HYPOGLYCEMIA

An abnormally low plasma glucose level that leads to symptoms of sympathetic nervous system stimulation or of CNS dysfunction.

For major causes of clinical hypoglycemia, see TABLE 13–5.

Pathophysiology

The brain depends on plasma glucose as its major metabolic fuel under most conditions. The blood-brain barrier excludes plasma albumin-bound free fatty acids (FFA), and the rate of ketone transport into the brain is too slow to meet its energy requirements unless the normal fasting plasma ketone body levels are markedly increased. Plasma glucose is normally regulated to maintain a level that ensures glucose transport into the brain at adequate rates.

Insulin does not regulate the activity of glucose in the brain. Centers within the CNS monitor plasma glucose levels and react to a potential deficiency by rapidly increasing adrenergic nervous system activity, resulting in epinephrine release. Additional neuroendocrine responses include increasing growth hormone and cortisol secretion and decreasing insulin secretion. Hepatic glucose output increases, and glucose use by nonneural tissues decreases. Adrenergic stimulation and glucagon (see below) play critical roles in the acute response to hypoglycemia, whereas growth hormone and cortisol secretion are delayed and less critical, but chronic deficiencies of these hormones can impair the normal counterregulatory response to hypoglycemia. If profound CNS glucose deficiency develops, higher brain center activity decreases to reduce brain energy requirements. If the hypoglycemia in unconscious patients is not treated rapidly, seizures and irreversible neurologic deficits or death may follow.

Glucagon is a polypeptide hormone secreted by α cells, found almost exclusively in the pancreatic islets in humans. In physiologic plasma levels, glucagon's effects are restricted to the liver, where it acutely increases hepatic glycogenolysis and glucose release into plasma; it also stimulates gluconeogenesis and activates the system that transports long chain FFA into hepatic mitochondria for oxidation and ketogenesis. Rare, isolated cases of persistent neonatal hypoglycemia have been ascribed to a relative glucagon deficiency associated with a relative hyperinsulinemia.

Classification

Hypoglycemia may be drug-induced (the most common cause) or nondrug-induced.

Drug-induced hypoglycemia: Insulin, alcohol, and sulfonylureas account for most of the hospitalized patients with hypoglycemia (see above under Complications of Insulin Treatment and under Oral Antidiabetic Drugs). **Alcoholic hypoglycemia** is characterized by impaired consciousness, stupor, or coma in a patient with a significantly elevated blood alcohol level and is primarily due to hypoglycemia. Hepatic alcohol oxidation increases the cytosolic ratio of reduced to oxidized nicotinamide adenine dinucleotide and inhibits hepatic glucose release by inhibiting the use of the major plasma gluconeogenic substrates (lactate, alanine) for glucose synthesis, resulting in a fall in plasma glucose that stimulates increases in plasma FFA and ketones. It is frequently associated with elevated plasma lactate and ketone levels and metabolic acidosis. The syndrome occurs in people who ingest alcohol after fasting long enough

TABLE 13–5. MAJOR CAUSES OF CLINICAL HYPOGLYCEMIA

Drug-induced (the most common cause)

Insulin, alcohol, and sulfonylureas account for > 50% of all hospitalized cases

Occasional causes: salicylates, propranolol, pentamidine, disopyramide, hypoglycin A (unripened akee fruit), quinine in falciparum malaria

Nondrug-induced

1. Fasting hypoglycemia
   - Characteristically present in infancy or childhood
     - Nesidioblastosis
     - Ketotic hypoglycemia
     - Inherited hepatic enzyme deficiencies that restrict hepatic glucose release: glucose-6-phosphatase; phosphorylase; pyruvate carboxylase; phosphoenolpyruvate carboxylkinase; fructose-1,6-diphosphatase; glycogen synthetase
     - Inherited defects in fatty acid oxidation, including systemic carnitine deficiency
     - Inherited defects in ketogenesis
   - Characteristically or more commonly present in adults
     - Islet cell adenoma or carcinoma
     - Hypoglycemia associated with large mesenchymal tumors
     - Autoimmune hypoglycemia in nondiabetics
     - Insulin-receptor antibody hypoglycemia
     - Severe liver disease
     - Severe renal disease
   - Less related to age
     - Cachexia
     - Endotoxic shock
     - Hypopituitarism with deficiency of both growth hormone and cortisol
2. Reactive hypoglycemia
   - Characteristically present in infancy or childhood
     - Hereditary fructose intolerance
     - Galactosemia
     - Leucine sensitivity
   - Characteristically present in adults
     - Alimentary hypoglycemia
     - Idiopathic alimentary hypoglycemia
     - Early-onset noninsulin-dependent diabetes mellitus (?)

to make their hepatic glucose output dependent on gluconeogenesis. Alcoholic hypoglycemia requires prompt treatment. *It can be induced by blood alcohol levels well below the common legal driving limit of 100 mg/dL (22 mmol/L).* Prompt improvement in the level of consciousness and subsequent resolution of the metabolic acidosis usually occur after a rapid IV infusion of 50 mL 50% glucose followed by IV 5% glucose in 0.9% sodium chloride solution (thiamine is usually added).

Other drugs that less commonly cause hypoglycemia include salicylates (most often in children), propranolol, pentamidine, disopyramide, and hypoglycin A, which is found in unripened akee fruit (causing a condition termed Jamaican vomiting sickness). Quinine is possibly a cause in patients with falciparum malaria.

Nondrug-induced hypoglycemia: Included are fasting hypoglycemia, characterized by CNS manifestations, usually during fasting or exercising, and reactive hypoglycemia, characterized by adrenergic symptoms that occur only when provoked by a meal. Reactive hypoglycemia is usually associated with less marked and briefer decreases in plasma glucose than fasting hypoglycemia. Some disorders that cause symptomatic hypoglycemia characteristically present in childhood or infancy, whereas others present more commonly in adulthood.

Causes of **fasting hypoglycemia** usually diagnosed in infancy or childhood include inherited liver enzyme deficiencies that restrict hepatic glucose release (deficiencies of glucose-6-phosphatase, fructose-1,6-diphosphatase, phosphorylase, pyruvate carboxylase, phospho*enol*pyruvate carboxykinase, or glycogen synthetase). Inherited defects in fatty acid oxidation, including that resulting from systemic carnitine deficiency, and inherited defects in ketogenesis (3-hydroxy-3-methylglutaryl-CoA lyase deficiency) cause fasting hypoglycemia by restricting the extent to which nonneural tissues can derive their energy from plasma FFA and ketones during fasting or exercise. This results in an abnormally high rate of glucose uptake by nonneural tissues under these conditions.

Ketotic hypoglycemia in infants and children is characterized by recurrent episodes of fasting hypoglycemia with elevated plasma levels of FFA and ketones, usually normal lactate levels, and low plasma alanine levels. In normal infants and young children, the duration of a fast required to cause an abnormally low plasma glucose level is much shorter than that for adults; in patients with ketotic hypoglycemia, this period is further reduced and is ascribed to a quantitative defect in the capacity to mobilize substrate for hepatic gluconeogenesis. Nesidioblastosis is characterized by a diffuse budding of insulin-secreting cells from pancreatic duct epithelium and pancreatic microadenomas of such cells; it is a rare cause of fasting hypoglycemia in infants and an extremely rare cause in adults.

Islet cell adenoma or carcinoma (insulinoma) is an uncommon and usually curable cause of fasting hypoglycemia and is most often diagnosed in adults. It may occur as an isolated abnormality or as a component of the type 1 multiple endocrine neoplasia (MEN) syndrome (see Ch. 10 and ENDOCRINE TUMORS in Ch. 34). Carcinomas account for only 10% of insulin-secreting islet cell tumors. Hypoglycemia in patients with islet cell adenomas results from uncontrolled insulin secretion, which may be clinically determined during fasting and exercise. Although absolute plasma insulin levels may not be greatly elevated, they may be inappropriately elevated in the context of hypoglycemia and prolonged fasting.

Hypoglycemia may also be caused by large non–insulin-secreting tumors, most commonly malignant mesenchymal tumors in the retroperitoneum or chest. The tumor secretes abnormal insulin-like growth factor (large IGF-II), which does not bind to its plasma binding proteins. This increase in free IGF-II exerts hypoglycemia through the IGF-I or the insulin receptors. The hypoglycemia is corrected when the tumor is completely or partially removed and usually recurs when the tumor regrows.

Extensive liver disease can cause fasting hypoglycemia. (Forms of cirrhosis other than cardiac rarely cause hypoglycemia.) **Autoimmune hypoglycemia** occurs rarely in nondiabetics, and the mechanism of hypoglycemia in this disorder is not understood. Patients with insulin-resistant diabetes due to insulin-receptor antibodies and acanthosis nigricans sometimes develop insulin-receptor antibodies that mimic insulin effects and cause fasting hypoglycemia.

Fasting hypoglycemia occasionally develops in patients with chronic renal failure; a specific cause is not usually identifiable. The development of renal disease in insulin-treated diabetics can cause hypoglycemia by decreasing renal insulin degradation and insulin requirements. Cachexia and endotoxic shock can cause fasting hypoglycemia at any age. Hypopituitarism with a deficiency of both growth hormone and cortisol can cause fasting hypoglycemia. Addison's disease (primary adrenocortical deficiency) rarely causes hypoglycemia in nondiabetics, unless they are starving, but it occurs with increased frequency in type 1 DM patients, in whom its development frequently causes hypoglycemia and decreases in insulin requirements.

In hereditary fructose intolerance, galactosemia, and leucine sensitivity of childhood, specific food components provoke **reactive hypoglycemia.** In hereditary fructose intolerance and galactosemia, an inherited deficiency of a hepatic enzyme causes acute inhibition of hepatic glucose output when fructose or galactose is ingested. Leucine provokes an exaggerated insulin secretory response to a meal and reactive hypoglycemia in patients with leucine sensitivity of childhood.

Reactive hypoglycemia associated with early-onset type II DM is characterized by adrenergic symptoms occurring 4 to 5 h after eating and is associated with an abnormally low plasma glucose level after an initial period of postprandial hyperglycemia. This is ascribed to a delayed and exaggerated rise in plasma insulin. Some practitioners question its existence.

Alimentary hypoglycemia is another form of reactive hypoglycemia that occurs in patients who have had prior upper GI surgical procedures (gastrectomy, gastrojejunostomy, vagotomy, pyloroplasty) and allows rapid glucose entry and absorption in the intestine, provoking excessive insulin response to a meal. This may occur within 1 to 3 hours after a meal. Very rare cases of idiopathic alimentary hypoglycemia occur in patients who have not had GI operations.

Symptoms and Signs

Hypoglycemia has two distinct patterns: (1) **Adrenergic symptoms** include sweating, nervousness, tremulousness, faintness, palpitations, and hunger attributed to increased sympathetic activity and epinephrine release (they can occur in adrenalectomized patients). (2) **CNS manifestations** include confusion, inappropriate behavior (which can be mistaken for inebriation), visual disturbances, stupor, coma, and seizures. Hypoglycemic coma commonly causes an abnormally low body temperature. Adrenergic symptoms usually start with acute, less marked decreases in plasma glucose than those that cause CNS manifestations, but the plasma levels at which symptoms of either type develop vary markedly among individual patients.

Diagnosis

Whether the patient presents with unexplained CNS manifestations or unexplained adrenergic symptoms, diagnosis requires evidence that the symptoms occur in association with an abnormally low plasma glucose level and are corrected by raising the plasma glucose. An abnormally low plasma glucose level is usually defined as < 50 mg/dL (< 2.78 mmol/L) in men or < 45 mg/dL (< 2.5 mmol/L) in women (below the lower limits seen in normal men and women after a 72-h fast) and < 40 mg/dL (< 2.22 mmol/L) in infants and children. (See also HYPOGLYCEMIA in Ch. 260.) Most cases of hypoglycemia occur in patients who have been treated with insulin or a sulfonylurea or who have recently ingested alcohol, and the diagnosis in such patients is rarely a problem.

Initial testing includes a rapid blood glucose test on any patient with unexplained impairment of consciousness (or seizures). If an abnormally low blood glucose level is found, glucose is rapidly infused (see Treatment, below); prompt improvement in the CNS manifestations with a rise in blood glucose (which occurs in most patients) confirms the diagnosis of fasting or drug-induced hypoglycemia. A portion of the initial blood sample should be saved as frozen plasma to determine the initial plasma insulin, proinsulin, and C-peptide levels or to perform a drug scan when necessary. Blood lactate and pH should be determined and the plasma checked for ketones.

Different causes may be distinguished by laboratory testing. Patients with insulin-secreting pancreatic tumors (insulinomas, islet cell carcinomas) usually have increased proinsulin and C-peptide levels that parallel the insulin levels. An increased C-peptide

level would be expected in patients taking a sulfonylurea, but a high level of the drug should be detectable. Patients with hypoglycemia induced by exogenous insulin injections (commonly health care workers or family members of a diabetic) have normal proinsulin levels and suppressed C-peptide levels. In the rare cases of autoimmune hypoglycemia, the plasma-free insulin during a hypoglycemic episode is usually markedly elevated, plasma C peptide suppressed, and plasma insulin antibodies readily detectable. Distinguishing autoimmune hypoglycemia from surreptitious insulin administration requires special studies.

Patients with an insulinoma differ from those with other causes of fasting hypoglycemia in that they frequently seek care for isolated episodes of sudden confusion or unconsciousness that have occurred for years and may have become more frequent. The episodes characteristically occur > 6 h after the last meal or after an overnight fast and are sometimes precipitated by exercise (eg, rapid walking before eating breakfast). They may resolve spontaneously, but a history of rapid improvement when the patient was given fluid or carbohydrates can frequently be elicited. A high plasma insulin level (> 6 μU/mL [> 42 pmol/L]) with hypoglycemia strongly suggests an insulin-secreting tumor if surreptitious use of insulin or a sulfonylurea can be excluded.

If other causes of episodic CNS symptoms are not apparent, the patient is hospitalized and subjected to a fast. Plasma glucose, insulin, proinsulin, and C-peptide levels are monitored. Within 48 h, 79% of patients with insulinomas develop symptoms, and 98% develop them within 72 h. The fast is terminated at 72 h or when symptoms develop. A presumptive diagnosis of an insulin-secreting tumor is warranted if the fast reproduces the patient's symptoms, which respond rapidly to glucose administration and are associated with an abnormally low plasma glucose level and an inappropriately high plasma insulin level. Other diagnostic procedures (eg, IV tolbutamide infusion) are rarely required and should be used only in experienced referral centers. Insulinomas are usually too small to be detected by standard x-rays or CT scans. Patients with a presumptive diagnosis should be sent to a referral center for evaluation by experienced physicians before any operation.

Alimentary hypoglycemia should be considered only in patients who have undergone prior upper GI surgical procedures and have postprandial adrenergic symptoms that are selectively corrected by ingesting carbohydrates. The relationship between the symptoms and the plasma glucose level is assessed by home blood glucose monitoring (eg, 1 and 2 h postprandially and whenever symptoms occur). *The oral glucose tolerance test (OGTT) is not valid for diagnosing alimentary hypoglycemia.*

Treatment

Oral ingestion of glucose or sucrose is usually adequate to relieve acute adrenergic symptoms and early CNS symptoms. Patients treated with insulin or a sulfonylurea are advised to drink a glass of fruit juice or water with 3 tbsp of table sugar added and to teach family members to give such treatment if they suddenly exhibit confusion or inappropriate behavior. A glass of milk also works well. Insulin-treated patients are advised to carry sugar lumps, candy, or glucose tablets at all times. In patients treated with a sulfonylurea, especially the long-acting ones such as chlorpropamide, hypoglycemia may recur over many hours or even days if oral intake is inadequate. When oral glucose is not available or adequate, IV glucose or glucagon may be used (see below).

IV injection of 50 or 100 mL of 50% glucose followed by a continuous infusion of 10% glucose (20% or 30% glucose may be needed) may be needed for severe symptoms or when a patient cannot take oral glucose. Blood glucose levels are monitored within a few minutes after the start of the 10% glucose infusion and frequently thereafter with a glucose analyzer, and the rate of infusion is adjusted to maintain a normal plasma glucose level. In children with CNS manifestations, treatment is started by infusing 10% glucose at a rate of 3 to 5 mg/kg/min, and the rate is adjusted to rapidly restore and maintain a normal plasma glucose level. *In general, pediatricians do not recommend the use of an IV bolus of 50% glucose or the use of IV fluids containing > 10% glucose in infants and children because they can have pronounced osmotic effects and, in some patients, may induce marked hyperglycemia and a marked stimulation of insulin secretion.* (See HYPOGLYCEMIA in Ch. 260 for treatment of hypoglycemia in newborns and infants.)

A **non–insulin-secreting mesenchymal tumor** frequently responds to surgical excision. However, the patient can remain free of symptomatic hypoglycemia for relatively long periods (sometime years) by frequently ingesting carbohydrates at bedtime and during the night. When surgical removal of most of the tumor is not feasible or when the tumor regrows to a large size with recurrence of fasting hypoglycemia, a gastrostomy may be needed for continuous feeding of enormous amounts of carbohydrate required throughout the day and night.

Glucagon is used to treat severe hypoglycemic reactions when oral glucose is inadequate and IV glucose is not available. It is mainly useful for emergencies away from medical settings. Glucagon is supplied in a kit containing powder that must be reconstituted with the diluent. The usual dose of glucagon in adults is 0.5 to 1 U given subcutaneously, intramuscularly, or IV; in children, it is 0.025 to 0.1 mg/kg (maximum dose, 1 mg). When glucagon is effective, manifestations of hypoglycemia usually subside within 10 to 25 min. If the patient does not respond to 1 U of glucagon within 25 min, further injections are unlikely to be effective and are not recommended. The major side effects are nausea and vomiting. The efficacy of glucagon is critically dependent on the size of hepatic glycogen stores; glucagon has little effect on plasma glucose in patients who have been fasting or hypoglycemic for a prolonged period.

An **insulin-secreting islet cell tumor** requires surgical treatment. Most often, a single insulinoma is found, and its enucleation is curative, but the tumor (or all of the tumors in the 14% of cases with multiple insulinomas) may not be located, resulting in a second operation or a blind partial pancreatectomy. Before the operation, diazoxide and octreotide (a long-acting octapeptic analog of somatostatin) may be used to inhibit insulin secretion. Patients with insulin-secreting islet cell carcinoma generally have a poor prognosis.

Hypoglycemia provoked by the ingestion of fructose, galactose, or leucine is treated by removing or limiting the offending substance. **Alimentary hypoglycemia** that occurs after a GI operation or that is idiopathic is managed with frequent small feedings of a high-protein, low-carbohydrate diet.

14 / THE PORPHYRIAS

A group of disorders caused by deficiencies of enzymes of the heme biosynthetic pathway.

Abnormally elevated levels of porphyrins or their precursors (eg, δ-aminolevulinic acid [ALA] and porphobilinogen [PBG]) are produced, accumulate in tissues, and are excreted in urine and stool. Disease manifestations result almost entirely from effects on the nervous system and skin.

The Heme Biosynthetic Pathway

Heme, an iron-containing pigment, is the nonprotein functional component of hemoproteins, which are found in all tissues.

The heme biosynthetic pathway is illustrated in FIG. 14–1. The eight different enzymes that drive the sequential steps in this pathway are numbered 1 through 8 in FIG. 14–1 and are briefly described below. The first enzyme and the last three are found in mitochondria; the intermediate enzymes occur in the cytosol.

1. ALA synthase, the first enzyme of the heme biosynthetic pathway, catalyzes the condensation of glycine and succinyl coenzyme A to form ALA. The enzyme is localized in the inner membrane of mitochondria and requires pyridoxal 5′-phosphate as a cofactor. Separate genes encode erythroid and nonerythroid ALA synthases.

2. ALA dehydratase, a cytosolic enzyme, converts two molecules of ALA into a monopyrrole, PBG, with the removal of two molecules of water. Lead inhibits ALA dehydratase activity by displacing zinc (the metal essential for enzyme activity) from the enzyme. The most potent inhibitor of the en-